REMARKS

Applicant respectfully requests reconsideration. Claims 1-73 were previously pending in this application. Claims 9, 10, 13, 17, 19, 22-38 and 41-73 were withdrawn. Applicant respectfully submits that the Office Action Summary incorrectly states under 4a) of the Office Action Summary, that claims 15-17 are withdrawn from consideration. While claim 17 was withdrawn, claims 15-16 were not, as correctly stated under 6) and in the Detailed Action. Applicant has amended claims 1-8, 11, 12, 14, 15, 18, 20, 21, 39 and 40 herewith without prejudice or disclaimer. Support for the amendments can be found in the claims as originally filed, for example, in claim 16 as originally filed, and throughout the specification, for example, in paragraph [0037] of the application as filed. Applicant has cancelled claim 16 herewith without prejudice or disclaimer. As a result, claims 1-8, 11, 12, 14, 15, 18, 20, 21, 39 and 40 are currently under examination.

Applicant submits herewith a Declaration by Dr. Marianne Brüggemann (Brüggemann Declaration).

Claim Rejections under 35 U.S.C. § 102/103

The Office has maintained the rejection of claims 1, 2, 4-6, 8, 11, 12, 14-16, 18, 20, 21, 39, 40 under 35 U.S.C. §102(e) as being anticipated by or in the alternative under 35 U.S.C. §103(a) as being obvious over Rajewsky et al. (USP 6,750,061). Office Action at page 3. The Examiner states that "Rajewsky discloses transgenic mice whose genome comprising targeted gene replacement of the mouse heavy chain immunoglobulin constant region genes with the human IgH constant region gene (e.g. see the abstract and claims 1-3). Hence the genome of these genetically modified mice does not contain a nucleic acid encoding an endogenous IgH constant region locus polypeptide, but contains all the IgH variable region, D and J segments." Office Action at page 3.

Applicant respectfully submits that Rajewsky teaches methods for the targeted replacement of a single gene within the ~200kb murine IgH C constant region, mCγ, with its human homologue, hCγ. Brüggemann Declaration at paragraphs 5 and 6. See also column 9 of US 6,570,061. Applicant respectfully submits that, contrary to the allegation of the Examiner, the targeted replacement of a single gene within the murine IgH C constant region according to the teachings of Rajewsky does not result in the instantly claimed modified mouse or mouse cell that

does not comprise a nucleic acid which itself encodes any endogenous IgH constant region locus polypeptide, but contains all the IgH variable region, D and J segments. Applicant submits that the murine IgH C constant region consists of eight genes (mCμ, mCδ, mCγ3, mCγ1, mCγ2B, mCγ2A, mCε, and mCα). Targeted replacement of mCγ1 with hCγ1, as taught by Rajewsky (see column 9 of US 6,570,061), accordingly, results in a modified animal that contains nucleic acids encoding seven endogenous constant region locus polypeptides (mCμ, mCδ, mCγ3, mCγ2B, mCγ2A, mCε, and mCα) and one exogenous (human) constant region locus polypeptide (hCγ1). Therefore, contrary to the statement made by the Examiner on page 3 of the Office Action, the resulting animal does "contain a nucleic acid encoding an endogenous IgH constant region locus polypeptide." In fact, the mice disclosed by Rajewsky contain seven intact IgHC constant region genes, each encoding a functional, endogenous polypeptide. Claim 1 of the instant application on the other hand requires that the mouse or mouse cell does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region locus polypeptide.

The Examiner alleges that the claims of the instant application "embrace mice having partial endogenous IgH C regions and/or having a human replacement IgH C region. Accordingly, the rejection still applies to these claims." Office Action at page 4. In response, Applicant respectfully submits that the phrase "genetically modified mouse or mouse cell characterized in that it does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region locus polypeptide", as recited in the amended claims of the instant application, refers to a mouse or mouse cell in which no functional endogenous product is made from the IgH C constant region locus. See, e.g., paragraphs 38 and 39 of the instant application. Accordingly, a genetically modified mouse referred to by this term is a mouse not expressing functional, endogenous mCμ, mCδ, mCγ3, mCγ2B, mCγ2A, mCε, and mCα polypeptide. As detailed above, Rajewsky teaches the generation of mice deficient in a single endogenous polypeptide only, while maintaining expression of functional endogenous polypeptides encoded by the non-targeted seven IgHC constant region genes (see, e.g., Figure 5a of US 6.570,061).

MPEP 2131 provides that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051,

1053 (Fed. Cir. 1987)." For at least the reasons detailed above and of record, Rajewsky does not describe each and every element of the invention as claimed. For example, Rajewsky does not describe a modified animal or cell that "does not contain a nucleic acid encoding an endogenous IgH constant region locus polypeptide, but contains all the IgH variable region, D and J segments", as recited in the claims of the instant application. Because Rajewsky does not teach each and every element of the instantly claimed invention, a rejection of the instant claims under 35 U.S.C. § 102(e) is inappropriate, and Applicant respectfully requests the rejection on these grounds to be withdrawn.

The Examiner has also maintained the objection for obviousness in view of Rajewsky under 35 U.S.C. §103 (a). We respectfully disagree with the Examiner.

MPEP 2142 provides that "[t]he Federal Circuit has stated that 'rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval)". The Patent Office has further implemented the holdings of *KSR* in MPEP 2143, providing that "[t]he key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit." MPEP 2142.

MPEP 2143 further provides that "the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper 'functional approach' to the determination of obviousness as laid down in *Graham*." MPEP 2143. The Examiner is required, under MPEP 2143, to formulate a rationale that may support a conclusion of obviousness. MPEP 2143 lists seven exemplary rationales:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. MPEP 2143.

Applicant respectfully submits that neither the instant nor the previous Office Action provide a clear articulation of the reasons why the claimed invention would have been obvious or articulate a rationale, consistent with *Graham* and *KSR*, to support a finding of obviousness, as required by the Patent Office's own guidelines set forth in MPEP 2143. The Examiner merely stated that "[i]t appears that the C region gene replacement claimed by Rajewsky embraces both a total or a partial replacement, wherein in the working examples, only one portion of the C region was replaced [...]. However, given the levels of the skilled as established by Rajewsky, one would have known how to make a mouse having total depletion of the endogenous IgH-C gene if one desires to do so. Thus, the claimed invention as a whole was at least *prima facie* obvious [...]." Office Action at pages 3-4.

The Office Action did not propose which rationale the finding of obviousness of the instantly rejected claims was based on. However, solely for the purpose of responding to the instant Office Action, Applicant submits that it appears that the Examiner may have concluded obviousness based on a rationale of some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the Rajewsky reference to arrive at the claimed invention, i.e., a rationale resembling rationale (G). MPEP 2143 provides that "[t]o reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Then, Office personnel must articulate the following:

> (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) a finding that there was reasonable expectation of success; and

(3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness." MPEP 2143 (emphasis added).

Applicant respectfully submits that neither the instant Office Action, nor the previous Office Action of record in this matter, has resolved the *Graham* factual inquiries or articulated any of the additional findings required to sustain a determination of obviousness as required by the MPEP guidelines. Further, the Office Action does not provide evidence for the allegations that (i) Rajewsky provides an enabling disclosure embracing total replacement, and (ii) that one of skill in the art would have known how to extrapolate the teachings of Rajewsky to arrive at the instant invention. Applicant respectfully submits that the finding of obviousness is, therefore, a mere conclusory statement, which, according to the Supreme Court's finding in *KSR*, as implemented into MPEP 2143, cannot sustain a finding of obviousness.

Applicant respectfully submits that one of skill in the art would not have extrapolated the teachings of Rajewsky to generate a genetically modified animal or cell that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region locus polypeptide. For example, it was well known to those of skill in the art at the time the invention was made that successful homologous recombination events depend, among other factors, on construct design and are also locus dependent. Brüggemann Declaration at paragraph 7. Genomic loci harboring highly repetitive sequences, such as the IgH C locus, are known to the person of ordinary skill in the art to be difficult to target as the repetitive sequences are likely to interfere in homologous recombination events. Brüggemann Declaration at paragraph 7. Neither the methods nor the constructs disclosed in Rajewsky are suitable to generate an animal that does not express any endogenous IgHC constant region polypeptide and Rajewsky does not teach the skilled person how to generate a construct or constructs that could successfully be used to generate a genetically modified animal or cell that does not express any endogenous immunoglobulin heavy chain constant region locus polypeptide. Brüggemann Declaration at paragraph 7. Neither the Rajewsky nor the Fell reference, nor the combination of both references, provides any guidance regarding a method to render the entire IgHC constant region locus non-functional.

Moreover, Rajewsky arguably teaches away from rendering the locus non functional.

In Rajewsky, it is preferred that transgenic animals are obtained that undergo affinity maturation and a class switch from the native immunoglobulin to a humanized form (column 3, paragraph 2). To do this, at least the endogenous IgHC μ region must be expressed (see columns 5 and 6). Thus, in view of Rajewsky, a skilled person would not be motivated to arrive at an animal as claimed in claim 1 because Rajewsky directs the skilled person to retaining the endogenous IgHC μ region.

In contrast to the methods taught by the Rajewsky and the Fell references, alone and in combination, the methods employed in the instant application to achieve inactivation of the entire Ig HC locus (all eight Ig HC genes) by deletion were performed by targeted integration of two different targeting constructs (each carrying a loxP site) into the mouse genome in a two-step targeting process. Brüggemann Declaration at paragraph 8. For Ig HC locus deletion, the loxP-sites were integrated at either end of the Ig HC locus on a single allele (tandem allele integration). Brüggemann Declaration at paragraph 8. Following successful generation of a mouse with both of the targeted integrations on the same allele, the mouse was bred with a Cre expressing mouse to obtain progeny in which the Ig HC locus flanked by loxP sites was deleted. Brüggemann Declaration at paragraph 8. Applicant submits that the instant application demonstrates for the first time how to make an animal or cell lacking endogenous IgH C constant region gene sequences to such an extent that no functional endogenous heavy chain polypeptide is made. Brüggemann Declaration at paragraph 10. Applicant submits that the methods used to achieve this would not have been obvious to the skilled person in view of the Rajewsky reference and the Fell reference, alone or in combination. Brüggemann Declaration at paragraph 10. Applicant further submits that those of skill in the art had no expectation of success in generating a genetically modified animal or cell that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region locus polypeptide by using methods and materials taught in the prior art including the Rajewsky reference. Brüggemann Declaration at paragraph 9. Until the production of the IgH C locus knock-out of the present invention it was uncertain that an animal or cell lacking endogenous IgH C constant region gene sequences to such an extent that no functional endogenous heavy chain polypeptide is expressed, but retaining one or more endogenous IgH V, IgH D and IgH J region genes, could be generated. Brüggemann Declaration at paragraph 9. Indeed, it was believed that "trans" recombination between endogenous V D J region sequences and constant region-like genes (e.g.

T cell receptor loci or pseudogenes) could lead effectively to reconstitution of endogenous constant region function. Brüggemann Declaration at paragraph 9. Further, it was expected that if such an animal could be generated, such an animal would not be viable, since it would be severely immunocompromised. Brüggemann Declaration at paragraph 9. Lack of expectation of success in using the methods taught in the prior art including the Rajewsky reference is further supported by scientific publications in the field, for example, by Brüggemann, M. (2004). *Human Monoclonal Antibodies from Translocus Mice*. Molecular Biology of B Cells. Eds Alt, Honjo and Neuberger. Elsevier. pp 547-561, previously submitted and re-submitted herewith, stating at page 557, left column that "[a] disadvantage of the various H chain silencing approaches is that V, D and in some cases J and C genes, are still present and allow their use in trans-switching, trans-splicing, and also translocation events".

In view of the deficiencies in the teachings of Rajewsky, the failure of the Office Action to articulate a rationale for a finding of obviousness, the absence of evidence supporting the mere conclusory statement of obviousness, and the evidence provided by Applicant regarding the lack of motivation and lack of feasibility to extrapolate the teachings of Rajewsky towards the instant invention, Applicant respectfully requests the rejection of claims 1, 2, 4-6, 8, 11, 12, 14-16, 18, 20, 21, 39, 40 under 35 U.S.C. §102(e) as being anticipated by or in the alternative under 35 U.S.C. §103(a) as being obvious over Rajewsky et al. (USP 6,750,061) to be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 1 and 7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Rajewsky et al. (USP 6,570,061) in view of Fell et al. (USP 5,202,238). Office Action at page 4. The Examiner asserts that "it would have been obvious to one of skill in the art [...] to modify the targeting vector as taught by Rajewsky et al, by simply substituting the enhancer with the one as taught by Fell, Jr. et al with a reasonable expectation of success. Office Action at page 4.

Applicant respectfully submits that the deficiencies of the teachings of Rajewsky, as analyzed in detail above and in remarks of record, cannot be overcome by "simply substituting the enhancer". Even with a substituted enhancer, the methods and constructs disclosed in Rajewsky are not suitable to generate an animal that does not express any endogenous IgHC constant region polypeptide and neither the teachings of Rajewsky alone nor the teachings of Rajewsky and Fell combined convey to the skilled person how to generate a construct or

constructs that could successfully be used to generate a genetically modified animal or cell that does not express any endogenous immunoglobulin heavy chain constant region locus polypeptide as discussed in detail above. Brüggemann Declaration at paragraphs 5-9. Fell does thus not remedy the shortcomings of Rajewsky. Moreover, the vectors used in Fell et al are classical replacement type gene targeting vectors. It is however known in the art (see paragraph [0056] of the present application) that these vectors are not suitable for targeting larger regions in excess of 20kb, let alone a region that spans 200kb.

Applicant respectfully submits that, similarly to the claim rejection over Rajewsky alone under 35 U.S.C. §102/103, the Office Action does neither resolve the *Graham* factual inquiries nor articulate a rationale, or any of the required findings under one of the exemplary rationales, that might support a finding of obviousness. The finding of obviousness is, thus, a mere conclusory statement. See MPEP 2143.

Because the combination of Rajewsky and Fell does not provide all of the elements of the claimed invention, and because the rejection of obviousness cannot be sustained absent evidence and rational arguments as required by MPEP 2143, as outlined above, Applicant respectfully requests the rejection of claims 1 and 7 on these grounds to be withdrawn.

Claim Rejections under 35 U.S.C. § 112

Claims 1-8, 11, 12, 14-16, 18, 20, 21, 39 and 40 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner stated that "the specification, while being enabling for making a genetically modified *mouse* lacking endogenous IgH constant region and containing the endogenous IgH VDJ region, does not reasonably provide enablement for making any non-human *mammal* having the recited features and it does not reasonably provide enablement for how to use the claimed invention." Office Action at page 5. Applicant respectfully requests reconsideration.

Without prejudice or disclaimer of any unclaimed subject matter, Applicant has amended the claims to recite the term "mouse" instead of the term "non-human mammal".

Further, the Examiner reiterated a statement made in the previous Office Action that "in view of the teachings of the specification, it reduces to produce two genetically modified mouse whose genome comprising a deletion of IgH constant gene (CΔ), wherein such deletion was lost in the second generation (see table 1, page 38), and hence, the specification fails to produce any

progeny of the (CΔ) mice." Office Action at page 5. In response, Applicant has previously submitted that Table 1 shows that the IgHC constant region deletion (CΔ) allele was not "lost" in the second generation, but that 4 mice of the second generation were homozygous (CΔ) mice. In response, the Examiner stated in the instant Office Action that "the Title of Table 4 [sic] is 'Transmission rate of Homologous integration and locus deletion'. However, the referred four mice in the row that shows locus deletion do not have homologous integration. The table is unclear as to what kind of locus deletion occurred in the four mice since the deletion does NOT appear to be the consequence of a homologous integration targeting event according to the description in the table." Office Action at page 7.

In response, Applicant submits that the description of Table 1 and the text in the specification relating to Table 1, for example, in paragraphs [0179]-[0180], describe that Table 1 lists the genotypes of mice in the two first generations of breeding germline transmitting mice (mice carrying one wild type allele and both targeting events on the other allele (wt/homologous integration, comprising two targeted loxP sites) with heterozygous Cre mice. This breeding scheme is a strategy well known to those in the art to produce a heterozygous recombinase-mediated deletion in the first generation and then generate homozygous mice carrying that deletion in the second generation. The number of mice of any of the four possible genotypes (CΔ/CΔ; homologous integration/CΔ; (homologous integration/wt; and wt/wt) are given. As clearly stated in the description of Table 1, the four homozygous (CΔ/CΔ) mice of the second generation were derived from the two heterozygous (homologous integration/CΔ) F1 mice obtained in the first generation. Therefore, the Examiner's statement that "such deletion was lost in the second generation" is incorrect and inconsistent with the description given in Table 1. The Examiner's statement in the instant Office Action that "the referred four mice in the row that shows locus deletion do not have homologous integration" is correct insofar as that these four mice do not show the undeleted, homologous integration allele (2 targeted loxP sites), but only the deletion allele (CΔ) after Cre-mediated recombination. However, this CΔ allele can only be achieved after Cre-mediated deletion of the homologous integration allele. The Examiner's conclusion that "[t]he table is unclear as to what kind of locus deletion occurred in the four mice since the deletion does NOT appear to be the consequence of a homologous integration targeting event", is, accordingly, incorrect, because the four homozygous CΔ mice have the Cre-mediated deletion version of the homologous integration allele. Thus, it is evident for those of ordinary

skill in the art that the deletion was the consequence of a homologous integration targeting event and subsequent Cre-mediated recombination of the targeted loxP sites.

Further, the Examiner states that "the specification fails to provide an enabling disclosure concerning how to use the claimed invention", because "it was unclear and the specification fails to teach whether the B-cells would reappear upon introducing Ig genes of foreign origin." Office Action at page 6.

In support of enablement, Applicant previously submitted a published article authored by Dr. Brüggemann addressing the issues raised by the Examiner. The Examiner stated in the instant Office Action that "the cited document is not enclosed as indicated and is not currently on record". Office Action at page 7. Applicant respectfully submits that the cited document, named M010670004US00-MISCREF4-JRV.pdf, was submitted via EFS on June 11, 2009. The Electronic Acknowledgement Receipt from June 11, 2009, EFS ID 5499292, available on PAIR, lists the cited document as Document Number 7, and the document is recorded and available on Private PAIR. For the convenience of the Examiner, Applicant re-submits the cited document herewith.

As can be seen at pages 555 to 556 of the enclosed review (Brüggemann, M. (2004). *Human Monoclonal Antibodies from Translocus Mice*. Molecular Biology of B Cells. Eds Alt, Honjo and Neuberger. Elsevier. pp 547-561), human Ig loci have been expressed in a background in which the endogenous mouse H and κ L chain loci have been rendered nonfunctional. Dr. Brüggemann states that the block in B-cell development "can be overcome by the introduction of an IgH translocus, which kick-starts B-cell development and leads to (human) antibody production." See page 556, left column.

Thus, practicing the claimed invention would not require undue experimentation for the person of skill in the art, given the level of skill and knowledge in the art, the nature of the invention as recited in the amended claims, and the guidance (including working examples) provided in the specification. In view of the foregoing evidence and arguments, Applicant submits that the claimed invention is enabled, and respectfully requests that the Examiner withdraw the rejection of claims1-8, 11, 12, 14, 15, 18, 20, 21, 39 and 40 on these grounds.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: February 16, 2010

Respectfully submitted,

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